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## Factors Associated with Postacute COVID-19 Syndrome Among Patients in Malaysia

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# Factors Associated with Postacute COVID-19 Syndrome Among Patients in Malaysia

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## Abstract

**Background:** Post-acute COVID-19 is known to affect multiple organs. It is essential to determine factors that affect post-acute COVID-19 syndrome and medications needed by patients for optimized care.

**Methods:** A prospective cohort study was conducted among patients recruited by stratified sampling from two COVID-19 hospitals in Malaysia. Patients were followed up for 6 months using a standard questionnaire to identify demographics, symptoms, medications taken, and factors associated with post-acute COVID-19 syndrome.

**Results:** A total of 388 were successfully followed up. The most frequently reported symptom was respiratory symptoms (N = 168, 43.30%), of which cough (N = 134, 34.54%) was the most common. After 12 weeks of follow-up, respiratory syndrome (N = 56, 14.43%) was frequently reported, of which cough (N = 41, 10.57%) was the most common. For respiratory syndrome, patients were commonly managed with diphenhydramine cough suppressants (N = 6, 1.55%, month 4) and metered dose inhaler (MDI) salbutamol (N = 7, 1.8%, month 4). The risk factors for post-acute COVID-19 syndrome were increased by 1.02 times (95% CI: 1.01, 1.04) with each advanced year of age and 2.87 times (95% CI: 1.51–5.48) in the presence of co-morbidities.

**Conclusions:** Post-acute COVID-19 causes multiorgan involvement, and symptoms may remain for months, with patients taking various medications. Patients with risk factors should be monitored closely for post-acute COVID-19 symptoms.

**Keywords:** medication, multiorgan, post-acute COVID-19, support, symptoms

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused 200 million infections globally, with more than 2 million infections recorded in Malaysia.<sup>1</sup> During infection, the virus affects multiple organs, which leads to various signs and symptoms, such as cough, fever, shortness of breath, sore throat, anosmia, ageusia, myalgia, chest pain, and headache during the initial infection.<sup>2</sup> Laboratory abnormalities with different organ involvement, such as lymphopenia, elevated levels of C-reactive protein, impaired liver profile, elevated erythrocyte sedimentation rate, and leukocytosis, have also been reported among COVID-19-infected individuals.<sup>3,4</sup> Despite the recovery, symptoms may persist, a condition termed postacute COVID-19, defined as the presence of symptoms in patients for more than four weeks or one month following a positive infection.<sup>5</sup> Postacute COVID-19 syndrome, alternatively, is defined as the persistence of symptoms for more than 12 weeks or three months.<sup>5</sup> The prevalence of postacute COVID-19 varies between 2% and 86%<sup>6</sup> of

those diagnosed with initial COVID-19 infection; however, the numbers can be underreported.

Similar to acute infection, postacute COVID-19 syndrome affects multiple organs, with various symptoms observed among patients.<sup>5</sup> Symptoms following recovery from the initial COVID-19 infection include cough and dyspnea (pulmonary sequelae), fatigue and myalgia (musculoskeletal sequelae), and chest pain and myocarditis (cardiovascular sequelae).<sup>5</sup> Alterations in laboratory findings, such as transaminitis, electrolyte imbalance, hematological abnormalities, and elevation of cardiac markers, can also be observed among patients with postacute COVID-19.<sup>5,7</sup> Moreover, neurological symptoms, such as headache, reduced concentration, and memory, psychiatric manifestations (anxiety, mood disorders, and insomnia), and alterations in the olfactory have been reported among these patients.<sup>5</sup>

Very often, patients continue to take medications to address postacute COVID-19 syndrome. Several papers documented the management of patients with postacute COVID-19, including symptomatic relief medications, such as paracetamol, and nonsteroidal anti-inflammatory drugs, for fever and proton-pump inhibitors for reflux.<sup>8</sup> Anticoagulant treatment has also been continued in patients with a thrombotic event during COVID-19, similar

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to the use of corticosteroids in individuals with organizing pneumonia.<sup>5,8</sup> Nonpharmacological management, such as aerobic exercises and breathing techniques, have been recommended for patients with respiratory symptoms.<sup>8</sup> However, limited reports are available regarding the treatment options for the management of complications associated with postacute COVID-19, especially in community settings.<sup>9</sup> The extent of patient medication to address the symptoms in the local setting is also unclear.

Determining factors that affect postacute COVID-19 syndrome may aid in the optimization of care for patients. The factors associated with postacute COVID-19 syndrome include gender, body mass index, and smoking status.<sup>10</sup> Female patients with a high body mass index and are smokers have a high risk of developing postacute symptoms. Moreover, existing comorbidities, previous admissions to critical care, and lack of vaccination predispose patients to postacute COVID-19 condition.<sup>9,10</sup> Regardless, studies demonstrating the factors associated with postacute COVID-19 syndrome among the local population are lacking. Patients at risk of post-COVID-19 infection must be identified to ensure continuous patient-centered care. Failure to address such issue can lead to further deterioration among patients, as observed in previous reports.<sup>5</sup> Therefore, the urgent need to address the continuous management of patients post-COVID-19 is important to ensure positive outcomes and reduce social and economic burden to the healthcare system.<sup>5</sup> As such, determining factors will allow for the improved management of newly diagnosed COVID-19 patients in the long run. Therefore, this study aimed to identify the occurrence, types of medication, and factors associated with postacute COVID-19 syndrome among the local population.

## METHODS

Before conducting this study, approval was obtained from the Medical Research and Ethics Committee, Ministry of Health Malaysia and University Kebangsaan Malaysia (UKM PPI/111/8/JEP-2022-190). This study was registered to the National Medical Research Registry (NMRR-21-754-59611) and conducted in accordance with the ethical standards mentioned in the 1964 Declaration of Helsinki. All patients included in the study provided an informed consent. Confidentiality was maintained throughout the study without any reference to a particular individual.

The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. Patients admitted in two COVID-19 hospitals between June 1<sup>st</sup>, 2021, and November 30<sup>th</sup>, 2021, were recruited in a prospective cohort study. The inclusion criteria were age 18 years and above, admission with a positive polymerase chain reaction test for COVID-19, being contactable during the 6-month study period, and informed consent. Patients with preexisting

psychiatric illnesses determined based on the clinician's diagnosis of incomplete medical data and lost to follow-up were excluded from the study. A stratified sampling method was used to reduce bias. Patients were randomly selected and stratified based on their wards. Randomization was performed using a random number generated using Microsoft Excel (Microsoft Corporation 2018). Cochran's sample size formula was used to calculate the sample size.<sup>11</sup> A minimum of 384 patients was needed based on a population size of 169 000 infected patients over six months in Malaysia (reported in MySejahtera, an application created by the Malaysian government to track COVID-19 patients in Malaysia), with 95% confidence interval (CI), 5% margin of error, and 50% response distribution.

Prior to data collection, the patients were initially screened in accordance with the inclusion criteria during ward admission. Those who had pre-existing psychiatric illness, as diagnosed by a clinician, and incomplete medical data were excluded. Data collection was then conducted in two stages: data collection for patients during hospitalization for stage 1 and follow-up of the same patients following discharge for stage 2. In stage 2, patients who were uncontactable during follow-up were subsequently excluded from the study. The demographic data collected comprised age, ethnicity, and gender. Secondary data from medical records of patients documented during hospitalization were used to collect information on obesity, vaccination status, the number of comorbidities, the number of medications taken by patients before hospitalization, the number of medications used during hospitalization, stages of COVID-19 infection, and symptoms that arose as results of COVID-19 infection.

Following discharge, the patients were followed up monthly for six months. The researchers collected the primary data of patients using standard questions in phone interviews. During each follow-up, the patients were interviewed to determine whether symptoms that were noted during admission lingered. The questions were answered with either a "Yes" or "No." The patients were then asked regarding any medications they were taking to address their symptoms. Responses were the name of the medication taken for each symptom.

The clinical outcome of the study was the incidence of postacute COVID-19 symptoms, postacute COVID-19 syndrome, and medications taken for postacute COVID-19 syndrome. Postacute COVID-19 symptoms were defined as symptoms lasting from 1 to 3 months. Postacute COVID-19 syndrome was defined as symptoms persisting beyond three months.<sup>5</sup>

Statistical Package for Social Science (version 28; IBM Corp., Armonk, N.Y., USA) was used for data analysis. Data on patient demographics, symptoms, and medication

were presented as frequencies and percentages. Simple and multiple logistic regression analyses were performed to determine the factors associated with postacute COVID-19 syndrome. Variables included in simple logistic regression with a  $p$ -value of  $<0.25$  were included in multiple logistic regression. A  $p$ -value of  $<0.05$  was considered significant.

## RESULTS

A total of 500 patients were recruited to participate in the study during hospitalization. From these patients, 112 patients were excluded due to having either passed away ( $N = 3$ , 0.6%) or being uncontactable ( $N = 109$ , 21.8%). Exactly 388 patients were successfully followed up for 6 months. The majority of recruited patients were Malay ( $N = 317$ ; 81.7%) and female ( $N = 261$ ; 67.3%), with an average age of  $48.8 (\pm 17.0)$  years. Slightly more than half were unvaccinated ( $N = 231$ ; 59.54%), and most recruited patients had comorbidities ( $N = 320$ ; 82.5%), with an average of two ( $\pm 2$ ) medications used in the past and eight ( $\pm 6$ ) medications used during hospitalization. Stage 3 COVID-19 infection was predominant among the recruited patients ( $n = 141$ ; 36.3%) (Table 1). Table 1 depicts the demographic findings on patients recruited in the study along with the stages of COVID-19 infection diagnosed and the number of medications used by patients.

### Postacute COVID-19 symptoms

More than half of the recruited patients ( $N = 231$ ; 59.53%) showed postacute COVID-19 symptoms between 1 and 3 months (Figure 1). Figure 1 shows the symptoms involving multiple organs and the trend of recovery in patients during the 6-month study period. The reported postacute COVID-19 symptoms were categorized into respiratory, gastrointestinal, neurological, musculoskeletal, and nonspecific symptoms. A total of 168 (43.30%) patients reported respiratory symptoms, of which cough ( $N = 134$ , 34.54%) was the most common. Gastrointestinal symptoms were reported in 42 (10.82%) patients, most of whom reported dyspepsia ( $N = 29$ , 7.47%). Fourteen (3.61%) patients reported postacute COVID-19 neurological symptoms, with headache ( $N = 9$ , 2.32%) as the most common symptom. A total of 28 (7.22%) patients reported postacute COVID-19 musculoskeletal symptoms, among which fatigue ( $N = 17$ , 4.38%) was the most common. Other symptoms, including infrequent, low-grade fever in the majority ( $N = 103$ , 26.55%), were reported in 117 (45.62%) patients.

### Postacute COVID-19 syndrome

Postacute COVID-19 syndrome was reported in 65 (16.75%) patients, with symptoms lasting for more than 3 months. A total of 56 (14.43%) patients reported respiratory syndrome, with cough ( $N = 41$ , 10.57%) as the most common symptom. Gastrointestinal syndrome was absent among patients with postacute COVID-19 syndrome. Neurological and musculoskeletal syndromes were reported in 5 (1.29%) and 8 (2.06%) patients, respectively. Other syndromes ( $N = 10$ , 2.6%) were also observed, with fever ( $N = 6$ , 1.5%) being the most commonly reported in patients with postacute COVID-19 syndrome.

**TABLE 1.** Demographic characteristics of patients included in the study ( $N = 388$ )

Demographic data	N (%)
Age	48.8 $\pm$ 17
<b>Ethnicity</b>	
Malay	317 (81.7)
Chinese	24 (6.2)
Indian	41 (10.6)
Others	6 (1.5)
<b>Gender</b>	
Male	127 (32.7)
Female	261 (67.3)
<b>Obesity status</b>	
Obese	170 (43.8)
Non-Obese	218 (56.2)
<b>Vaccination status</b>	
Complete vaccination	115 (29.6)
Partial vaccination	42 (10.8)
Unvaccinated	231 (59.5)
<b>Comorbidities</b>	
Yes	320 (82.5)
No	68 (17.5)
Comorbidities	1.63 $\pm$ 1.205
No. of medication prior to admission	2 $\pm$ 2
No. of medication on admission	8 $\pm$ 6
<b>Stages of COVID-19</b>	
1	15 (3.9)
2	82 (21.1)
3	141 (36.3)
4	125 (32.2)
5	25 (6.4)

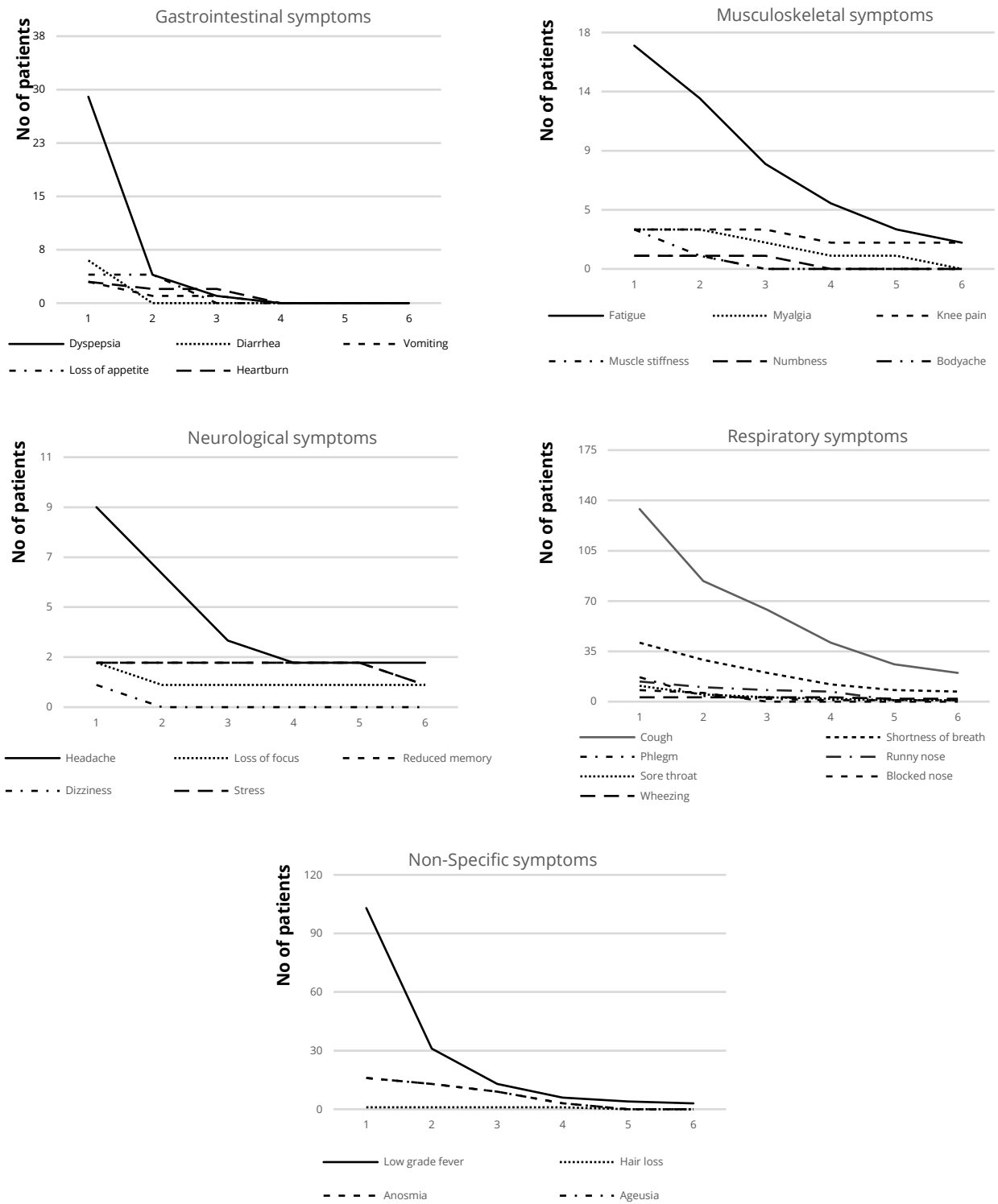


FIGURE 1. Symptoms of postacute COVID-19 over 6 months

**TABLE 2.** Medications used for the management of postacute COVID-19 (N = 388)

Characteristics	Months, N (%)					
	1	2	3	4	5	6
<b>Respiratory symptoms</b>						
Diphen-hydramine	47 (12.12)	19 (4.90)	13 (3.35)	6 (1.55)	5 (1.29)	3 (0.77)
Cough mixtures	19 (4.90)	15 (3.86)	11 (2.84)	3 (0.77)	2 (0.52)	2 (0.52)
Chlorpheniramine	5 (1.29)	4 (1.03)	2 (0.52)	2 (0.52)	1 (0.26)	1 (0.26)
Prolase	4 (1.03)	3 (0.77)	3 (0.77)	2 (0.52)	1 (0.26)	1 (0.26)
Turbuhaler budesonide/fenoterol	1 (0.26)	1 (0.26)	1 (0.26)	1 (0.26)	1 (0.26)	1 (0.26)
MDI salbutamol	8 (2.06)	8 (2.06)	7 (1.80)	7 (1.80)	5 (1.29)	5 (1.29)
MDI budesonide	4 (1.03)	4 (1.03)	4 (1.03)	4 (1.04)	3 (0.77)	3 (0.77)
MDI ipratropium/fenoterol	1 (0.26)	1 (0.26)	1 (0.26)	1 (0.26)	1 (0.26)	1 (0.26)
<b>Neurological symptoms</b>						
Paracetamol	8 (2.06)	4 (1.03)	1 (0.26)	1 (0.26)	1 (0.26)	1 (0.26)
<b>Musculoskeletal symptoms</b>						
Paracetamol	2 (0.77)	1 (0.26)	1 (0.26)	1 (0.26)	1 (0.26)	0 (0.00)
<b>Other symptoms</b>						
Paracetamol	87 (22.42)	27 (6.96)	11 (2.84)	6 (1.55)	4 (1.03)	3 (0.77)

**TABLE 3.** Factors associated with postacute COVID-19 syndrome (simple logistic regression)

Variables	OR (95% CI)	p
Age	1.02 (1.00, 1.04)	0.01
Male (Female)	1.15 (0.66, 2.01)	0.62
<b>Ethnicity (Malay)</b>		
Indian	0.93 (0.41, 2.28)	0.93
Chinese	0.42 (0.10, 1.85)	0.25
Others	0.00 (0.00, 0.00)	1.00
Obese (Non-obese)	0.36 (0.20, 0.66)	0.00
<b>Vaccination (Vaccinated)</b>		
Partially vaccinated	1.57 (0.61, 4.02)	0.35
Nonvaccinated	1.49 (0.79, 2.82)	0.22
Comorbidities (No comorbidities)	0.43 (0.23, 0.80)	0.01
No. of medication prior to admission	0.97 (0.86, 1.09)	0.60
No. of medication on admission	1.03 (0.99, 1.08)	0.16
<b>Stages of COVID-19 (Stage 1)</b>		
Stage 2	1.34 (0.27, 6.60)	0.72
Stage 3	1.14 (0.24, 5.41)	0.87
Stage 4	1.38 (0.29, 6.60)	0.68
Stage 5	2.05 (0.36, 11.80)	0.42

**TABLE 4.** Factors associated with postacute COVID-19 syndrome (multiple logistic regression)

Variables	AOR (95% CI)	p
Age	1.02(1.01, 1.04)	0.00
Comorbidities (No comorbidities)	2.87 (1.51, 5.48)	0.00

**Medications for postacute COVID-19 symptoms**

Table 2 shows the medications taken for the first 3 months of postacute COVID-19 symptoms. The most common medications were diphenhydramine for respiratory symptoms (N = 47, 12.12, month 1) and paracetamol (N = 8, 2.06%; N = 2, 0.77%; N = 87, 22.42%, month 1) for neurological, musculoskeletal, and other systems.

**Medications for postacute COVID-19 syndrome**

In postacute COVID-19 syndrome lasting for 4–6 months, the most common respiratory pharmacological management involved diphenhydramine cough suppressants (N = 6, 1.55%, month 4) and metered dose inhaler (MDI) salbutamol (N = 7, 1.8%, month 4), which continued until month 6. However, for the first 3 months, the patients were initially on various medications, such as diphenhydramine, cough mixtures, heder helix, bromhexine, loratadine and its combinations, chlorpheniramine, prolase, lozenges, benzydamine gargle, turbuhaler budesonide/fenoterol, MDI salbutamol, MDI budesonide, and MDI ipratropium/fenoterol. No medications were used for gastrointestinal syndrome among the study population, although pantoprazole, diphenoxylate/atropine, oral rehydration salts, loperamide, metoclopramide, and vitamin B complex were reported for the initial 3 months of postacute COVID-19 gastrointestinal symptoms. For postacute COVID-19 neurological syndrome, paracetamol (N = 1, 0.26%, month 4) was used until the 6th month and for the first 3 months of symptoms. A few medications, such as methyl salicylate liniments, tramadol/orphenadrine, multivitamins, and vitamins B1, 6, and 12, were initially used for musculoskeletal symptom although only paracetamol was continued for postacute COVID-19 musculoskeletal syndrome (N = 1, 0.26%, month

4) until month 5. Similarly, for other postacute COVID-19 syndromes, patients often reported the use of paracetamol (N = 6, 1.55%, month 4) until month 6 for the management of fever and pain, although diclofenac was also used in the first month.

### Factors associated with postacute COVID-19 syndrome

Table 3 shows the results of simple logistic regression analyses of factors contributing to postacute COVID-19 syndrome. A simple logistic regression of patients' characteristics was performed to determine the factors associated with postacute COVID-19 syndrome, which are defined as symptoms that persist beyond 3 months.<sup>5</sup> Advanced age, presence of comorbidities, and obesity increased the odds of developing postacute COVID-19 syndrome ( $p < 0.05$ ). Table 4 shows the results of multiple logistic regression analyses of factors contributing to postacute COVID-19 syndrome. Multiple logistic regression was performed on variables with a  $p < 0.25$  in simple logistic regression, and a significant relationship was observed between age and comorbidities. An increase in age by one year increased the odds of developing postacute COVID-19 syndrome by 1.02 (95% CI: 1.01–1.04) times. In the presence of comorbidities, the patients were 2.87 (95%CI: 1.51–5.48) times likely to develop postacute COVID-19 syndrome. The Hosmer and Lemeshow test value for fitness was 0.74 and showed good fit of the model.<sup>12</sup> The results of logistic regression showed statistical significance, with an area under the receiver operating characteristic curve of 0.6, which demonstrates the acceptable capability of the model to predict postacute COVID-19 syndrome occurrence.<sup>13</sup>

## DISCUSSION

Postacute COVID-19 respiratory symptoms, such as cough and dyspnea, which eventually progress to respiratory syndrome, were commonly observed among patients in the study population. This finding is similar to those of previous work,<sup>5</sup> with less frequent symptoms, such as runny nose, persistent sore throat, blocked nose, and wheezing.<sup>14,15</sup> Despite the high incidence of persistent cough following discharge, a substantial reduction occurred within 5 months, with other studies reporting an average of up to 11 days and 7 months for cough symptoms to subside.<sup>16</sup> However, other symptoms, such as shortness of breath, phlegm, runny nose, and sore throat, improved considerably within 2–3 months, which is a shorter period compared with the 7 months observed in previous studies.<sup>17</sup> Apoptosis and airway epithelial damage 3–6 months post-COVID-19 infection were observed,<sup>17</sup> consistent with the occurrence of symptoms among patients. As such, many patients continued to seek symptomatic treatment, including the use of antihistamines, antitussive, and anti-inflammatory medications, following discharge, similar to the findings of previous reports.<sup>8</sup> The symptomatic treatment frequently

used by patients in the study included diphenhydramine for cough, bromhexine for phlegm, and pseudoephedrine for blocked nose, which are often obtained from community health centers.<sup>18,19</sup>

An increase in age was among the factors associated with postacute COVID-19 syndrome. Elderly patients are at risk for persistent symptoms, which possibly trigger or exacerbate chronic conditions that commonly occur in older people, such as cardiovascular diseases, respiratory diseases, neurodegenerative conditions, and functional decline.<sup>20</sup> The elderly have low levels of T-cells and high levels of memory T-cells, predisposing them to aggravated infection and poor outcomes.<sup>21</sup> Moreover, alterations in immune-mediated inflammatory response during infection with sustained activation of the immune system lead to postacute COVID-19 symptoms.<sup>21</sup> In addition, elderly patients may exhibit a prominent increase in the presence of cellular changes without repair.<sup>21</sup> Aging has been strongly associated with frailty, which leads to postacute COVID-19 syndrome,<sup>21,22</sup> which often reduces the quality of life of patients.<sup>23</sup>

The presence of comorbidities also increased the risk of postacute COVID-19. This result was similar to previous findings.<sup>9,24,25</sup> Patients with multiple comorbidities admitted to critical care developed postacute COVID-19 condition 2.5 times more than their counterparts,<sup>9</sup> similar to that observed in the current work. Preexisting illness has been proposed to aggravate the postacute COVID-19 condition as this results in an increased risk of organ injury caused by immune-mediated sequelae, reduction in virus clearance, exacerbated inflammation, and reduced ability of the patient to tolerate injury to organs.<sup>24,26</sup> Moreover, patients with comorbidities are predisposed to prolonged hospitalization and need intensive care,<sup>26</sup> which in turn leads to postacute COVID-19 syndrome,<sup>27,28</sup> supporting the current findings. As such, patients with comorbidities are often monitored more closely in the event of a COVID-19 infection because of the intense management that may be required.<sup>25</sup>

The current work provides insights into the factors of postacute COVID-19 among patients. After discharge, many still face health challenges for up to 6 months. In some cases, symptoms may persist for longer than the study period. At the time of the study, vaccinations were still in the early stages of implementation, and as such, a high number of patients were still not fully vaccinated. Regardless, vaccination status was not a factor of postacute COVID-19 syndrome occurrence, similar to previous reports;<sup>23</sup> this finding highlights the importance of continued postacute COVID-19 monitoring in the population. Among the limitations of the current study was the duration of follow-up for up to 6 months, in which some symptoms may have not fully resolved. In addition, a few patients did default on their follow-up, which required them to be excluded from the study. These

patients either did not respond to phone calls, changed their number or passed away during the data collection. The collected data of the patients were removed and data was not included into the findings. Notably, despite their high number, the different comorbidities present in the study population could not be categorized into appropriate groups due to the low numbers in each category. As such, the use of comorbidities present in the analysis limited our ability to determine those that were most associated with postacute COVID-19 syndrome. Further work using a larger sample size can be performed to determine the association among the types of comorbidities and the risk of postacute COVID-19 syndrome. As with all questionnaire-based surveys, the results of the study were dependent on the honesty of patients throughout the study period and their ability to correctly remember their medications during the interview. The researcher questioned patients on the symptoms that occurred during admission and were still present during the interview and the medications they had taken. However, as the interview was conducted only once a month, some information may have been forgotten, which may have limited our findings. Therefore, generalization should be performed with caution. Despite this issue, the current work demonstrated the need for continuous care of patients post-COVID-19. Postacute COVID-19 demonstrated a multisystem involvement, with patients resorting to over-the-counter medication for relief. As such, a multidisciplinary approach is essential as a part of the follow-up process to ensure individualized treatment and address patient needs.

## CONCLUSIONS

Postacute COVID-19 affected more than half of the study population for months after initial infection, with patients requiring various symptomatic approaches to address respiratory, gastrointestinal, musculoskeletal, and neurological symptoms. Patients affected by factors, such as advanced age and the presence of comorbidities, should be given close attention because of their higher risk of developing postacute COVID-19 syndrome. The need for long term care is highlighted in the current work with postacute COVID-19 occurring months after initial infection. As such, healthcare professionals should be aware of the long-term effects of COVID-19 to ensure optimum management of these patients. The role of healthcare professionals should also be extended to primary care, including the need to monitor the use of medications for symptomatic relief. Emphasis should be made on ensuring interactions between multidisciplinary teams to ensure continuity of care is provided.

## CONFLICT OF INTEREST

None declared.

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